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EL 913014816 US  
Express Mail Label NumberNovember 20, 2001  
Date of Deposit

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

OKUNO ET AL.

APPLICATION NO:

FILED:

FOR: PHARMACEUTICAL COMPOSITIONS AND USES

Assistant Commissioner for Patents  
Washington, D.C. 20231PRELIMINARY AMENDMENT

Sir:

Prior to calculation of the filing fees, please amend the application as follows:

## IN THE SPECIFICATION

Under the Title and before the first line, please insert - -This is a continuation of International Application No. PCT/EP00/04562, filed May 19, 2000, the contents of which are incorporated herein by reference.- -

## IN THE CLAIMS

6. (Amended) A method according to claim 1, wherein the patient is suffering from inflammation, myocardial ischemia, rheumatoid arthritis, osteoarthritis and tumour growth, invasion or metastasis.

7. (Amended) A method according to claim 1, in which the bisphosphonate is selected from the following compounds or a pharmaceutically acceptable salt thereof, or any hydrate thereof: 3-amino-1-hydroxypropane-1,1-diphosphonic acid (pamidronic acid), 3-(N,N-dimethylamino)-1-hydroxypropane-1,1-diphosphonic acid, 4 amino-1-hydroxybutane-1,1-diphosphonic acid (alendronic acid), 1-hydroxy-ethidene-bisphosphonic acid, 1-hydroxy-3-(methylpentylamino)-propylidene-bisphosphonic acid, ibandronic acid, 6-amino-1-hydroxyhexane-1,1-diphosphonic acid,

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3-(N-methyl-N-n-pentylamino)-1-hydroxypropane-1, 1-diphosphonic acid, -1-hydroxy-2-(imidazol-1-yl)ethane-1,1-diphosphonic acid; 1-hydroxy-2-(3-pyridyl)ethane-1,1-diphosphonic acid (risedronic acid), including N-methyl pyridinium salts thereof, for example N-methyl pyridinium iodides such as NE-10244 or NE-10446; 1-(4-chlorophenylthio) methane-1,1-diphosphonic acid (tiludronic acid), [e.g. tiludronate;] 3[N-(2-phenylthioethyl)-N-methylamino]-1-hydroxypropane-1,1-diphosphonic acid; 1-hydroxy-3-(pyrrolidin-1-yl)propane-1,1-diphosphonic acid, 1-(N-phenylaminothiocarbonyl)methane-1,1-diphosphonic acid, 5-benzoyl-3,4-dihydro-2H-pyrazole-3,3-diphosphonic acid tetraethyl ester, 1-hydroxy-2-(imidazo[1,2-a]pyridin-3-yl)ethane-1,1-diphosphonic acid, and 1,1-dichloromethane-1,1-diphosphonic acid (clodronic acid).

8. (Amended) A method according to claim 1, in which the bisphosphonate is pamidronic acid or zoledronic acid, or a pharmaceutically acceptable salt thereof, or any hydrate thereof.

#### Remarks

The claims have been amended to eliminate multiple dependencies. A marked-up version of the claims with markings to show changes made is attached hereto.

Early and favorable consideration of the application is respectfully requested.

Respectfully submitted,

  
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Date: November 20, 2001

## **MARKED-UP VERSION OF CLAIMS WITH MARKINGS TO SHOW CHANGES MADE**

### **IN THE SPECIFICATION**

Under the Title and before the first line, please insert - - This is a continuation of International Application No. PCT/EP00/04562, filed May 19, 2000, the contents of which are incorporated herein by reference.- -

### **IN THE CLAIMS**

6. (Amended) A method according to claim 1 [or a use according to claim 2 or 3 for the treatment of angiogenesis in a] wherein the patient is suffering from inflammation, myocardial ischemia, rheumatoid arthritis, osteoarthritis and tumour growth, invasion or metastasis.
7. (Amended) A method according to claim 1 [or a use according to claim 2 or 3,] in which the bisphosphonate is selected from the following compounds or a pharmaceutically acceptable salt thereof, or any hydrate thereof: 3-amino-1-hydroxypropane-1,1-diphosphonic acid (pamidronic acid), [e.g. pamidronate (APD);] 3-(N,N-dimethylamino)-1-hydroxypropane-1,1- diphosphonic acid, [e.g. dimethyl-APD;] 4 amino-1-hydroxybutane-1,1-diphosphonic acid (alendronic acid), [e.g. alendronate;] 1-hydroxy-ethidene-bisphosphonic acid, [e.g.-etidronate;] 1-hydroxy-3-(methylpentylamino)-propylidene-bisphosphonic acid, ibandronic acid, [e.g. ibandronate;] 6-amino-1- hydroxyhexane-1,1-diphosphonic acid,[e.g. amino-hexyl-BP;] 3-(N-methyl-N-n-pentylamino)-1-hydroxypropane-1, 1-diphosphonic acid, [e.g. methyl-pentyl-APD (=BM 21,0955);]-1-hydroxy-2-(imidazol-1-yl)ethane-1,1-diphosphonic acid; 1-hydroxy-2-(3-pyridyl)ethane-1,1-diphosphonic acid (risedronic acid),[e.g. risedronate,] including N-methyl pyridinium salts thereof, for example N-methyl pyridinium iodides such as NE-10244 or NE-10446; 1-(4-chlorophenylthio) methane-1,1-diphosphonic acid (tiludronic acid), [e.g.tiludronate;]3[N-(2-phenylthioethyl)-N-methylamino]-1-hydroxypropane-1,1-diphosphonic acid; 1-hydroxy-3-(pyrrolidin-1-yl)propane-1,1-diphosphonic acid, [e.g. EB 1053 (Leo);] 1-(N-phenylaminothiocarbonyl)methane-1,1-diphosponic acid, [e.g. FR 78844 (Fujisawa);] 5-benzoyl-3,4-dihydro-2H-pyrazole-3,3-diphosphonic acid tetraethyl ester, [e.g. U-81581 (Upjohn);] 1-hydroxy-2-(imidazo[1,2-a]pyridin-3-yl)ethane-1,1-diphosphonic acid, [e.g. YM529; and 1,1-dichloromethane-1,1-diphosphonic acid (clodronic acid), [e.g. clodronate].
8. (Amended) A method according to claim 1 [or a use according to claim 2 or 3], in which the bisphosphonate is pamidronic acid or zoledronic acid, or a pharmaceutically acceptable salt thereof, or any hydrate thereof.